

Chlorpromazine-induced Hyperprolactinemia in a Young Female and Its Relation with Fibrocystic Breast Disease

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ABSTRACT:

Chlorpromazine-induced hyperprolactinemia in a young female and its relation with fibrocystic breast disease

We report the case of a 20 year old unmarried female patient who has been diagnosed as schizophrenia with intellectual disability. Patient was on chlorpromazine since last three years subsequently develop hyperprolactinemia, later manifested into fibrocystic breast disease. Hyperprolactinemia, is known for decades as neglected side effect of antipsychotic medication. Prolactin is secreted in a pulsatile manner by the anterior pituitary gland. The main physiological function of prolactin is to cause breast enlargement and galactorrhea initially and later develop to fibrocystic breast disease. Routine investigation also revealed hypothyroidism. Prolactin is known as immunomodulator, and has been linked to benign or malignant tumor growth.

Keywords: hyperprolactinemia, hypothyroidism, chlorpromazine, fibrocystic breast disease

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INTRODUCTION

Hyperprolactinemia is a condition of elevated serum prolactin. Prolactin is a 198 amino acid protein produced in lactotroph cells of anterior pituitary glands. All conventional antipsychotics blocks D2 receptors on lactotroph cells and thus remove the main inhibitory influence on prolactin secretion. Elevation of prolactin levels occurs within a few hours of treatment initiation (1). All antipsychotic causes significant changes in prolactin levels but some do increase prolactin above normal range at standard dosage. These

drugs are chlorpromazine, risperidone, clozapine, olanzapine, and aripiprazole (2-4). Persistent elevation of plasma prolactin is associated with number of adverse consequences; these includes sexual dysfunction (5), reduction in bone mineral density (6), breast enlargement and galactorrhea (7), suppression of hypothalamic pituitary gonadal axis (8), and possible increase in the risk of breast cancer (3,9,10,11). Apart from hyperprolactinemia, other adverse effects, induced by first generation antipsychotics are extrapyramidal side effects, including rigidity, bradykinesia, dystonia, tremor, and akathisia. Common

side effects are anticholinergic, sedation, weight gain; uncommon ones are galactorrhea, hyperprolactinemia, ejaculatory disorder, and blood dyscrasia; rare ones are seizure and cholestatic jaundice.

The role of prolactin in both men and women is diverse. Elevated level may be as a result of physical exertion, medications, pituitary adenoma, and renal failure (12). A normal prolactin level in female 72–511 millionth of international unit per milliliter (uiu/ml) and for male 53–360 millionth of international unit per milliliter (uiu/ml).

Dopamine receptors in the hypothalamus are critical component of the negative feedback system for hormones such as prolactin which is released by pituitary gland (3), if dopamine receptors are blocked by antipsychotics, the hypothalamus continues to stimulate the pituitary gland to produce and secrete prolactin leads to hyperprolactinemia.

The hyperprolactinemia is due to dopamine antagonist, and antipsychotics were studied in large numbers of women. The patient's taking dopamine antagonist had 16 percent increase in the rate of breast cancer either benign (fibrocystic breast disease) or malignant. The prolactin levels associated with individuals on antipsychotics for both male and female are much higher than normal expected levels. Women have significantly greater prolactin level than men during chronic antipsychotic treatment with equivalent doses (13). Low daily dosing of chlorpromazine 200 mg can cause significant prolactin elevations (1) and level have been increase in dose-dependent manner up to 600 mg chlorpromazine (14). The physiological function of prolactin is to cause breast enlargement, lactation and may lead to complication like fibrocystic breast disease. The patient who have extremely high prolactin level may have been given bromocriptine, it lowered the initial prolactin level but did not bring the level down to the normal range, one of the theoretical concern for clinicians is that bromocriptine antagonizes the effect of antipsychotics and potential to exacerbate psychotic symptoms. Bromocriptine has approved indication of acromegaly, hyperprolactinemia, hypothyroidism, type 2 diabetes mellitus and Parkinson's disease (15). The dopamine agonist such as bromocriptine reduce hyperprolactinemia even though some studies show they did not benefit breast cancer treatment, however, dopamine antagonists such as chlorpromazine and other antipsychotics increase hyperprolactinemia. Several studies have been reported in association of hyperprolactinemia with hostility, anxiety, and depression

in women, although the severity of these symptoms appears to be mild.

CASE REPORT

A 20 years old, unmarried female with good body built suffering from psychiatric illness, was admitted in our chronic rehabilitation ward since around 6 years long. She was diagnosed with schizophrenia with intellectual disability. She has a history of intellectual disability since childhood, later developed psychosis. She was on multiple antipsychotics like risperidone, aripiprazole, amisulpride, and olanzapine but it was for short duration and patient was not stable on it, so switched to chlorpromazine due to fear of metabolic side effects but last was on chlorpromazine since 3 years. She was stable on chlorpromazine 200 mg twice a day. Her psychotic symptoms and disturbed behavior were much reduced with chlorpromazine. Her brief psychiatric rating scale (BPRS) score was 27 with an absence of psychotic symptoms, it was 62 before starting chlorpromazine. Patient developed enlarged breasts, galactorrhea, and feeling discomfort in both breast and became irritable.

The laboratory examination showed normal free triiodothyronine (FT3) and free thyroxine (FT4) but Thyroid stimulating hormone (TSH) 12.59 uiu/ml and prolactin level 3,132.72 uiu/ml. The brain magnetic resonance imaging showed an unremarkable pituitary gland and other investigations were within normal limits. Chlorpromazine was tapered, stopped, and put on thyroxine 75 microgram per day along with bromocriptine 2.5 milligram per week. Prolactin level was again monitored after a month, it still remain increased 1,999.77 uiu/ml. On examination, pain and discomfort was observed in both breasts, which were swollen, lumpy, and movable lumps on both sides and had secretion without any pressure. Patient had been referred to surgery department, there biopsy was done, histopathology report revealed fibrocystic breast disease, no malignancy detected and bilateral inferior pedicle reduction mammoplasty was performed. After the surgery, antipsychotic changed to quetiapine 100 mg twice a day along with long acting injection fluphenazine decanoate 50 mg per 15 days due to her disturbed behavior such as increased irritability, anger outburst, and disturbed sleep. At present patient is maintaining well with no recurrence of hyperprolactinemia.

DISCUSSION

In our patient the hyperprolactinemia was due to a conventional antipsychotics like chlorpromazine. All antipsychotics, causes significant changes in prolactin but some do normally increase prolactin above normal range at standard dose like chlorpromazine. Peptides, steroids, and neurotransmitters regulate the synthesis and release of the hormone prolactin from the lactotrophs of the anterior pituitary. The most important hypothalamic prolactin-inhibiting factor is dopamine. Dopamine acts as a tonic inhibitor of prolactin secretion through the tuberoinfundibular, the tuberohypophysial dopaminergic systems (16). The binding of dopamine to the D2 receptors on the membrane of the lactotroph cells inhibits the prolactin gene transcription, synthesis and release of prolactin, and lactotroph proliferation (16). On the other hand, D2 receptor blockade by antipsychotics counteracts the tonic inhibitory effect of dopamine on prolactin secretion, thus elevating serum prolactin levels.

On the basis of clinical findings, insidious onset with enlargement and feeling of discomfort in both breasts with discharge was observed. On physical examination breast showed swollen, lumpy, and movable lumps on both side and had secretion without any pressure. Prolactin level was increased to 3,132.72 uIU/ml, so we diagnose a case of

chlorpromazine-induced hyperprolactinemia and we found its correlation with hypothyroidism as thyroid stimulating hormone level was also increased to 12.59 uIU/ml. A positive correlation of 1:4 was found between hypothyroidism and hyperprolactinemia. Patient has been given thyroxine for her hypothyroidism and bromocriptine to decrease prolactin level, but did not get satisfactory improvement. Patient was referred to surgical consultation, where breast biopsy was done, and histopathology report revealed fibrocystic breast disease and bilateral inferior pedicle mammoplasty was performed.

CONCLUSIONS

This case report indicates the possibility of hyperprolactinemia due to chlorpromazine, as patient was on chlorpromazine 200 mg twice per day since long around 3 years on stable dose. Dopamine antagonist increase production of prolactin, which is mitogenic, suppresses apoptosis, and stimulates breast cancer growth. It was suggested that patients with benign breast lumps and pain should be screened for clinical or laboratory evidence of hyperprolactinemia. Patient who have raised prolactin levels along with fibrocystic breast disease should be regularly followed up as they may be prone to develop breast cancer due to multiple risk factors combination.

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